Proton Transfer Reactions of N-Aryl Triazolium Salts: Unusual Ortho-Substituent Effects

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**ABSTRACT:**

Previous studies of the C(3)-hydrogen/deuterium exchange reactions of the triazolium ion conjugate acids of triazolyl NHCs revealed a change of mechanism under acidic conditions with N1-protonation to a dicationic salt. Interestingly, the data suggested an increase in $pK_a^{N1}$ in the presence of a N-pentafluorophenyl substituent relative to other N-aryl substituents with hydrogens or methyl substituents rather than fluorines at the ortho-positions. To probe this apparent donor effect of a N-pentafluorophenyl substituent, which differs from the more common electron withdrawing effect of this group, we have studied the analogous deuterium exchange reactions of four triazolium salts with heteroatoms or heteroatom substituents in the 2- and/or 6-positions of the N-aryl ring. These include triazolium salts with N-2,4,6-tribromophenyl 11, N-2,6-dichlorophenyl 12, N-2-pyridyl 13 and N-2-pyrimidinyl 14 substituents. The log $k_{ex}$ – $pD$ profiles for 11, 12 and 14 were found to show similar trends at lower $pDs$ as for the previously studied N-pentafluorophenyl triazolium salt, hence supporting the presence an apparent donor effect on $pK_a^{N1}$. Surprisingly, the log $k_{ex}$ – $pD$ profile for N-pyridyl salt 13 uniquely showed acid catalysis at lower $pDs$. We propose herein that this data is best explained by invoking an intramolecular general base role for the N-(2-pyridyl) substituent in conjunction with N1-protonation on the triazolium ring. Finally, the second order rate constants for deuteroxide-ion catalyzed C(3)-H/D exchange ($k_{DO}$, M$^{-1}$s$^{-1}$), which could be obtained from data at $pDs > 1.5$, were used to provide estimates of C(3)-carbon acid $pK_a^{C3}$ values for the four triazolium salts 11 – 14.
INTRODUCTION

Triazol-3-ylidenes 1 form a class of stable N-heterocyclic carbenes (NHC) that are frequently utilized as efficient, selective organic catalysts in a broad range of transformations.\textsuperscript{[1-7]} Closely related to other stable NHCs including imidazole-2-ylidenes 2, imidazolin-2-ylidenes 3, thiazol-2-ylidenes 4 and trihydropyrimidin-2-ylidenes 5, these carbenes have seen application in diverse areas of chemistry in addition to organic catalysis.\textsuperscript{[8-17]} Common to most applications of NHCs of this type is the \textit{in situ} generation of the carbene from the conjugate acid azolium salt precursor by use of an appropriate base. We and others have reported the kinetic acidities towards hydroxide ion and estimates of the aqueous pK\textsubscript{a} values of the conjugate acid precursors to NHCs 1-5.\textsuperscript{[18-23]}

\[
\begin{array}{cccc}
\text{RN} & \text{NR'} \\
\text{1} & \text{RN} & \text{NR'} \\
\text{2} & \text{RN} & \text{NR'} & \text{S} \\
\text{3} & \text{RN} & \text{NR'} \\
\text{4} & \text{RN} & \text{NR'} \\
\text{5} & \text{RN} & \text{NR'} \\
\end{array}
\]

In particular, we showed that the pD rate profiles for the deuterium exchange reactions of triazolium salt precursors 6 to triazol-3-ylidenes 7 reveal distinct differences from analogous data for NHCs 2-5.\textsuperscript{[21]} The presence of the additional ring nitrogen in triazolium ions 6 allows for alternative deuterium exchange mechanisms under more acidic conditions. Deuteronation at N(1) can occur to give dicationic triazolium ions 8, which are precursors to monocationic N-heterocyclic carbenes 9. At higher pD values, log $k_{ex}$ values were observed to increase linearly with pD consistent with a first order dependence on deuteroxide ion and exchange via triazol-3-ylidenes 7 (Path A, Scheme 1). At lower pD values, upward deviations were observed from the line of unit slope through the log $k_{ex}$ – pD data consistent with a change in mechanism for deuterium exchange.
Scheme 1 Potential Mechanistic Pathways for Deuterium Exchange at C(3)-H of Triazolium Ions 6.

Of the large series of triazolium salts studied in aqueous solution, the altered dependence of log \( k_{ex} \) values on pD under more acidic conditions was most prevalent, and occurred at significantly higher pD values, for N-pentafluorophenyl triazolium salt 6a (Ar = C\(_6\)F\(_5\)).\(^{[21]}\) For the structurally homologous series of triazolium salts 6, the pD value for onset of the change in slope decreased in the order 6a > 6b > 6c > 6d ~ 6e ~ 6f (Ar = C\(_6\)F\(_5\) (a); 4-CN-Ph (b); 4-F-Ph (c); H (d); 2,4,6-(Me\(_3\))-Ph (e); 4-MeO-Ph (f)). Only in the case of triazolium salt 6a was the initial decreased dependence on pD further followed by a downward break at the lowest pDs studied. Data for 6a could be fit by an equation describing either of two kinetically equivalent mechanistic options (Paths B or C, Scheme 1), which both require protonation at N1 of the triazolium ring. Path B involves a solvent promoted deuterium exchange reaction of the cationic triazolium salt 6a with removal of active species via N-protonation to a dicationic triazolium ion 8a. Path C entails no solvent reaction of the monocationic
salt 6a, but instead the initial N-protonation at N(1) of salt 6a followed by deuterioxide-catalyzed exchange on the dicationic triazolium salt 8a. Both of these mechanisms allow for the observed continued decrease in $k_{ex}$, the first order rate constants for deuterium exchange, with $pD$. Based on an analysis of the results of fitting through assumption of either pathway, we suggested that Path C was the more likely option.

In order to explain the differences in the observed kinetic data for 6a-f, we postulated that the presence of an ortho-heteroatom, e.g. fluorine, could favour protonation (or deuteronation) at N(1) resulting in an increased prevalence of dicationic triazolium salts 8 in the normal $pD$ range. Of the substrates studied, only the N-pentafluorophenyltriazolium salt 6a had ortho-heteroatoms rather than hydrogen or methyl groups on the N-aryl ring. A higher $pK_a$ (N1) for salt 6a seems counter-intuitive based on the electron-withdrawing, through-bond, inductive substituent effect of fluorine, which would be expected to decrease basicity at N(1). However, protonation at N(1) may be favoured in order to suppress unfavourable electrostatic interactions between this nitrogen and spatially proximal N-aryl ortho-fluorines, or, as a result of stabilizing through-space $N^+\cdot\cdot\cdot\text{ortho-F}$ interactions in the N-protonated salt.

In related mechanistic studies of triazolium catalysis of benzoin and Stetter reactions by triazolium salts, we have also observed unexpected substituent effects in the presence of ortho-heteroatom substituents on the N-aryl ring of catalyst. The common first step of both of these reactions involves the reaction of an aryl aldehyde and triazolium salt in the presence of base to give a deuteroxy aryl intermediate 10 (Scheme 2, shown for benzoin condensation). We have observed that N-aryl ortho-X-heteroatom substituents significantly increase rate and equilibrium constants for formation of adducts 10 relative to para-substituted and ortho-alkyl analogues. One possible explanation of these observations is the presence of an O-D…X interaction in the adduct similar to the $N^+\cdot\cdot\cdot\text{ortho-F}$ interaction proposed above.
Scheme 2 Triazolium Catalysis of the Benzoin Condensation.

In order to further probe these ortho-substituent effects, we have studied the deuterium exchange reactions of a number of additional triazolium salts 11-14 with heteroatoms or heteroatom substituents in the 2- and/or 6-positions of the N-aryl ring. The data for these substrates also provides further evidence that Path C, and not Path B, is accountable for the altered dependence of log $k_{ex}$ values on $pD$ under more acidic conditions. In addition, we observed that the $N$-pyridyl triazolium salt 13 displays a different $N$-aryl substituent effect to all other triazolium substrates. Formal acid catalysis of deuterium exchange was uniquely observed for $N$-pyridyltriazolium salt 13 under more acidic conditions, providing evidence for a possible intramolecular deprotonation reaction involving the pyridyl substituent.

EXPERIMENTAL
The syntheses of triazolium salts 11-14, the preparation of solutions, the determination of $pD$ and NMR methods are described in the Supporting Information.

Kinetic measurements
The kinetic procedures for the measurement of rate constants for deuterium exchange for triazolium salts 11-14 were identical to those previously reported for the study of
analogous salts. Due to the lability of the triazolium salts towards C(3)-H/D-exchange in unbuffered D₂O solvent, reactions were initiated by addition of a solution, containing internal standard (tetramethylammonium deuteriosulfate) and buffer or DCl, directly to the rigorously dried triazolium salt. The final substrate and internal standard concentrations in the D₂O reaction solutions were 5 mM and 1 mM, respectively. Reaction solutions in NMR tubes were incubated at 25 °C in a thermostatted water bath. pD values were recorded at the beginning and end of each reaction and were found to be constant within error (± 0.05). The progress of the C(3)-H/D deuterium exchange reaction was followed by 1H NMR spectroscopy during the disappearance of 75-90% of the C(3)-H signal of each substrate. There was no change in the integrated areas of signals due to all other protons of triazolium salts during this period, and no appearance of new signals, consistent with the absence of any parallel decomposition or hydrolysis reactions under the reaction conditions. For N-pyrimidinyl salt a competing reaction was observed to occur to a small extent accounting for ≤ 6% of total products. Based on the NMR signals due to the products formed, this reaction was presumed to be a nucleophilic aromatic substitution reaction of DO⁻ or D₂O at C(2) of the pyrimidinyl ring.

The observed pseudo first order rate constants for exchange of the C(3)-proton for deuterium, \( k_{\text{ex}} \) (s⁻¹), were obtained from non-linear least square fitting of reaction progress against time to a first order exponential decay function. Reaction progress was defined by values of \( f(s) \), the fraction of remaining unexchanged substrate, which were calculated from Eqn. (1), where \( A_{\text{C3H}} \) and \( A_{\text{std}} \) are the integrated areas of the singlet due to the C(3)-H of the triazolium salt and the broad triplet at 3.3 ppm due to the methyl hydrogens of internal standard, tetramethylammonium deuteriosulfate. In the case of triazolium salt 14, small corrections were made for the parallel S_NAr reaction of substrate such that the corrected \( f(s) \) values represented reaction due to deuterium exchange only.

\[
f(s) = \frac{(A_{\text{C3H}} / A_{\text{std}})_t}{(A_{\text{C3H}} / A_{\text{std}})_0}
\]

Representative NMR spectral overlays of the deuterium exchange reactions, first order kinetic plots, tabulated \( k_{\text{ex}} \) data and log \( k_{\text{ex}} - pD \) rate profiles are included in the Supporting Information for each triazolium salt 11-14 (Figures S1-S16, Tables S1-S4).
RESULTS AND DISCUSSION

The C(3)-H/D deuterium exchange reactions of triazolium salts 11-14 were performed in aqueous acetic acid buffer or DCl solutions at a range of pD values and at constant ionic strength, \( I = 1.0 \) (KCl). For these substrates, deuterium exchange was too fast to monitor above pD 4 at 25 °C. Buffer catalysis of deuterium exchange was found to be insignificant in all previous studies of azolium ion conjugate acids of N-heterocyclic carbenes including representative triazolium salts.\(^{18, 20, 21}\) Hence, it was assumed that buffer catalysis of exchange was not significant and the observed pseudo first order rate constants for exchange, \( k_{ex} \) (s\(^{-1}\)) were used directly on pD - rate profiles of deuterium exchange.

As in the previous study of a large series of triazolium salts, values of log \( k_{ex} \) for 11 and 12 (Figure 1, ▲ and ▼) increase with pD in the region from pD = 0 to 4.5. Figure 1 shows the pD rate profiles for these salts in comparison with those for two previously studied N-pentafluorophenyl and N-phenyl triazolium salts 6a and 6d, respectively. Figure 2 shows the pD rate profiles for N-pyridyl and N-pyrimidinyl salts 13 and 14 also in comparison with previous data for 6a and 6d, respectively. The data for N-pyridyl triazolium salt 13 (Figure 2, ◦) was distinctly different from all other triazolium salts studied including N-pentafluorophenyl substrate 6a. Values of log \( k_{ex} \) for 13 decrease with pD in the region from pD = 0 to 1.3 and increase with pD in the region 1.3 - 4.5. By contrast, the log \( k_{ex} \) – pD profile for N-pyrimidinyl salt 14 (Figure 2, ◇) is comparable to those for 11 and 12 displaying an increase of rate constants for exchange with pD in the whole region studied.

Deuterium Exchange Reactions of N-2,4,6-Tribromophenyl- 11 and N-2,6-Dichlorophenyl- 12 Triazolium Tetrafluoroborates

Deuterium exchange kinetic data for N-2,4,6-tribromophenyl- and N-2,6-dichlorophenyl triazolium salts 11 and 12 show the same dependencies on pD as observed for N-pentafluorophenyl salt 6a. In particular, there is a marked change in the dependence of log \( k_{ex} \) values on pD under more acidic conditions closely similar to data for 6a and more significant than for 6b-6f. At pDs > 1.5, values of log \( k_{ex} \) for 11 and 12 increase linearly with pD and the data may be fit by a line of unit slope indicating a first order dependence on deuteroxide ion concentration in this region.
This is consistent with a mechanism involving deuteroxide-catalyzed C3-H/D exchange of the monocationic triazolium ion substrate (Path A, Scheme 1). At pDs < 1.5, the dependencies of log $k_{ex}$ on pD decrease and data points in this region deviate upwards from the line of unit slope that fits the remaining data at higher pDs. There is also the beginning of a further downward break at the lowest pD values as observed previously for N-pentafluorophenyltriazolium salt 6a. By comparison, the profile for unsubstituted N-phenyl salt 6d (Figure 2, □) is essentially linear with slope unity for all data points except at pDs < 0.2.

As in our previous study for 6a, the data for salts 11 and 12 fit well to a kinetic scheme allowing for the occurrence of either Paths B or C at lower pDs in conjunction with Path A at higher pDs. The log $k_{ex}$ − pD data fits well to Eqns. (2) or (3) which allow for Paths A and B or Paths A and C, respectively. In these equations, $k_{DO}$ (M$^{-1}$s$^{-1}$) is the second order rate constant for deprotonation of monocationic triazolium ion (c.f. 6, Scheme 1) by deuteroxide, $K_w = 10^{-14.87}$ is the ion product of D$_2$O at 25 °C, $\gamma_{DO} = 0.73$ is the activity coefficient for deuteroxide ion under our experimental conditions, $K_a^N$ is the acidity constant for ionization at N, $k_{D2O}$ (s$^{-1}$) is the first order rate constant for deprotonation of monocationic triazolium ion at C(3) by solvent D$_2$O and $k_{DO}$' (M$^{-1}$s$^{-1}$) is the second order rate constant for deprotonation of dicationic triazolium ion (c.f. 8, Scheme 1) by deuteroxide ion. Fitting to either equation yields identical values for $k_{DO}$ and $K_a^N$ (Table 1), whereas values for $k_{D2O}$ or $k_{DO}$' are obtained by fitting to Eqn. (2) or Eqn. (3), respectively (Table 2). For comparison, previously reported data$^{[21]}$ for N-pentafluorophenyl and phenyl salts 6a and 6d are also included in Tables 1 and 2.

$$\log k_{ex} = \log \left[ \frac{K_a^N \left( \frac{k_{DO} K_w}{\gamma_{DO}} \right) 10^{pD} + \left( K_a^N k_{D2O} \right)}{\left( K_a^N + 10^{-pD} \right)} \right]$$  \hspace{1cm} (2)

$$\log k_{ex} = \log \left[ \frac{K_a^N \left( \frac{k_{DO} K_w}{\gamma_{DO}} \right) 10^{pD} + \left( k_{DO} K_w \right)}{\left( K_a^N + 10^{-pD} \right)} \right]$$  \hspace{1cm} (3)
Values of the second order rate constants, $k_{DO}$, for C(3)-deprotonation by deuterioxide ion of triazolium salts 6a, 6d, 11 and 12 decrease in the order 6a > 11 > 12 > 6d although the difference across this series is only 10-fold (Table 1). Similarly small N-aryl substituent effects were observed for the twenty triazolium salts previously studied with $k_{DO}$ values only varying by a maximum of 37-fold across this large series. The order of reactivity of triazolium salts corresponds to an increase in rate constant for deprotonation at C(3) with more electron-withdrawing N-aryl substituents.

The acidity constants for protonation at nitrogen, $K_a^N$, increase in the order 6a < 11 < 12 and correspond to p$K_a^N$ values of 0.18, 0.04, 0.01, respectively (Table 1). The relatively large fitting errors associated with these $K_a^N$ values are expected as only ~50% N-protonation has occurred at pH = 0. The values for p$K_a^N$ are very similar within error, and the data shows that there is a small increase in the degree of N-protonation within the normal pH range in the order 12 < 11 < 6a. Importantly, as observed previously for 6a, the p$K_a^N$ values for 11 and 12 must be substantially higher than for N-phenyl salt 6d (Figure 2) and other N-aryl salts 6b-f. The pD profiles for 6b-f are linear through most of the pD region studied, with only a few data points showing upward deviation, suggesting no substantial protonation at N1 and lower p$K_a^N$ values. In particular, the profiles for N-4-cyanophenyl 6b and 2,6-dichlorophenyl 12 substrates are almost superimposable at pDs > 1.5 yielding similar $k_{DO}$ values (Figure S17), however, the altered dependence on pD is greater for 12 under more acidic conditions. As the electronic substituent effect on $k_{DO}$ is similar in both cases, this supports the existence of an additional ortho-chloro substituent effect to explain the observed differences in p$K_a^N$. This N-aryl net donor effect on p$K_a^N$ for 6a, 11 and 12 is opposite to the normal inductive through-bond electron accepting substituent effect of these substituents, which would favour an increase in acidity and decrease in p$K_a$ as observed at C(3). Instead, we observe an increase in the basicity of N(1) in the presence of ortho-fluoro, bromo and chloro substituents relative to other N-aryl triazolium ions 6b-f.

Previously,[21] we suggested that Path C rather than B was the most likely mechanism under more acidic conditions to explain the altered dependence of log $k_{ex}$ values on pD. This was mainly based on a comparison of rate constants for deuterium exchange for triazolium ion 6a with analogous literature data for thiazolium ions 15.[23, 25] There is no additional site for protonation within the thiazolium ring of 15.
unlike for the triazolium analogue 6a. Washabaugh and Jencks did observe the onset of a true pD-independent solvent reaction for four thiazolium salts 15 in concentrated DCI solutions at pDs << 0 yielding rate constants, \( k_{D2O} \), that range from \( 1.6 \times 10^{-9} \) s\(^{-1} \) up to \( 9.4 \times 10^{-8} \) s\(^{-1} \). In a comparison of data for triazolium and thiazolium salts, we previously noted that the difference in \( k_{DO} \) values is significantly smaller than for \( k_{D2O} \) values. As an example, \( k_{DO} = 4.67 \times 10^7 \) M\(^{-1}\)s\(^{-1} \) for the N-cyanomethyl thiazolium salt 15 (\( R_1 = \text{CN}, R_2 = \text{H} \)), which is 14-fold lower than \( k_{DO} = 6.82 \times 10^8 \) M\(^{-1}\)s\(^{-1} \) for N-pentafluorophenyltriazolium salt 6a (Table 1), whereas there is a much greater 650-fold difference for the corresponding \( k_{D2O} \) values [\( k_{D2O} = 9.4 \times 10^{-8} \) s\(^{-1} \) for 15 (\( R_1 = \text{CN}, R_2 = \text{H} \)) versus \( k_{D2O} = 6.1 \times 10^{-5} \) s\(^{-1} \) for 6a (Table 2)]. It is difficult to explain a substantially larger ring effect on the solvent compared with the deuteroxide-catalyzed deuterium exchange reactions, and, we suggested that this provides evidence that Path B is not the correct mechanism to account for our data at low pDs. Further, the N-protonated dicationic substrate would be expected to be more acidic at C(3) than the monocationic analogue, and it seems logical (due to the requirement for N-protonation to explain the observed log \( k_{ex} - pD \) data for 6a) that a deuteroxide reaction of the dication would be more likely than a water reaction on the monocation given the greater reactivity of both the substrate and the base in the former case, albeit at very low concentrations of DO\(^-\).

![Diagram](image)

The new data in Table 2 for triazolium salts 11 and 12 supports these conclusions. The \( k_{D2O} \) values calculated for 11 and 12 using Eqn. (2) are 85 – 213-fold larger than observed for the true pD-independent solvent reactions of the N-cyanomethyl thiazolium salt 15 (\( R_1 = \text{CN}, R_2 = \text{H} \)), whereas there is a much smaller ring effect on \( k_{DO} \) values (< 10-fold), again suggesting that Path B does not occur for the former triazolium ions. Estimates for \( k_{DO} \) calculated for C(3)-deprotonation of the dicationic conjugate acids of 11 and 12 (c.f. 8 in Scheme 2), for reaction via Path C, are all at the diffusional limit (Table 2). This is logical given that \( k_{DO} \) values for the less reactive monocationic salts are already as high as \( \sim 10^8 \) M\(^{-1}\)s\(^{-1} \). Further, as will be
seen below, the observed acid catalysis in the case of \textit{N}-pyridyl salt 13 is most logically accounted for in tandem with Path C for the other triazolium salts at lower pDs.

\textit{Deuterium Exchange Reactions of N-Pyridyltriazolium 13 and N-2,6-Pyrimidinyl-14 Triazolium Tetrafluoroborates}

As for triazolium salts 11-12, values of log $k_{ex}$ for \textit{N}-pyridyl salt 13 increase linearly at pD s $> 1.5$ (Figure 2, ♦), and the data may be fit by a line of unit slope consistent with a first order dependence on deuteroxide ion concentration in this region and deuterium exchange via Path A (Scheme 1). In contrast with data for the other triazolium salts in Figure 1, values of log $k_{ex}$ for 13 decrease with pD in the region from pD $= 0$ to 1.3. This observed acid catalysis of deuterium exchange requires protonation of substrate and a subsequent pD-independent C(3)-deprotonation of the resulting dicationic substrate.

The log $k_{ex}$ – pD data for \textit{N}-pyridyl salt 13 fits well to Eqn. (4), which allows for both deuteroxide-catalyzed exchange on the monocationic triazolium salt (Path A, Scheme 1) and, additionally, a pD-independent C(3)-deprotonation reaction on the dicaticonic substrate. In Eqn. (4), $k_{DO}$, $K_w$ and $\gamma_{DO}$ are as defined above. The first order rate constant $k'$ (s$^{-1}$) refers to pD-independent deprotonation of dicaticonic substrate and mechanistic options for this process are discussed below. In this case, either the pyridyl nitrogen or N1 of the triazolium ring could potentially be protonated to give a dicaticonic species. The pK$_a^N$ = -0.05 calculated for \textit{N}-pyridyl substrate 13 (Table 1) is similar to pK$_a^N$ values for triazolium salts 6a, 11 and 12 for which additional protonation can only occur at N(1) of the triazolium ring. However, pK$_a^N$ = -0.05 may also be consistent with the acidity constant for the pyridinium nitrogen. Numerous solution studies establish the pK$_a$ of the N-protonated pyridinium ion at ~5$^{[26]}$ and this would be expected to substantially decrease in the presence of a monocationic triazolium substituent.
Possible mechanisms formally consistent with the observed acid catalysis of deuterium exchange for N-pyridyl salt 13 at lower pDs are shown in Scheme 3. In analyzing these options, a key consideration is whether these mechanisms can explain why a pD-independent reaction of N-protonated salt is possible for 13 but has not been observed for any other triazolium ion. Option D1 (Scheme 3) involves initial protonation on N1 of the triazolium ring followed by pD-independent deprotonation by D₂O without direct involvement of the pyridyl ring. This mechanism may be discounted as acid catalysis of deuterium exchange has not been observed for any other triazolium ion studied to date, and a remote pyridyl substituent would not be expected to drastically increase the rate of deprotonation of dicationic substrate by solvent, especially as $k_{DO}$ values for exchange via Path A (Scheme 1) are similar for 13 and other triazolium salts studied.

**Scheme 3** Potential Mechanistic Options for pD-independent deprotonation of a dicationic N-deuterated N-pyridyl triazolium salt.

\[
\log k_{ex} = \log \left( K_a^N \left( \frac{k_{DO}K_w}{\gamma_{DO}} \right) 10^{pD} \right) + k' \left( 10^{-pD} \right) \tag{4}
\]
Option D2 (Scheme 3) involves initial protonation on the pyridyl nitrogen, rather than N1 of the triazolium ring, followed by pD-independent deprotonation by water. Remote protonation on the adjacent pyridyl ring would not significantly increase the rate of deprotonation at C(3) by solvent to enable competition with Path C (Scheme 1). The latter would be expected to be faster due to N1-protonation on the more proximal triazole ring with subsequent C(3) deprotonation by more basic deuteroxide ion. N-protonation of the pyridyl substituent could, in theory, increase the rate of deprotonation by water at C(3) to compete with a water reaction of the monocationic triazolium salt (Path B, Scheme 1)). However, the data for all other triazolium salts requires protonation at N1, as the pD-rate profiles do not show pD-independence and log \( k_{ex} \) values continue to decrease, hence, this latter option is self-contradictory. Protonation of the more proximal triazolium ring should then also result in a competing water reaction like D1 above and acid catalysis would also be expected for the other triazolium salts. On this basis, Option D2 cannot account for the unique observation of acid catalysis for 13 in competition with either Path B or C for the other triazolium salts.

Another possibility is that a shared hydrogen bond forms between N1 on the triazole and the pyridyl nitrogen thereby accelerating the rate of deprotonation at C(3) by solvent (Option D3, Scheme 3). However, due to the non-linear geometry, this hydrogen bond would be expected to be weak. Also, it is difficult to envisage why this would occur only for a solvent deprotonation reaction and not for deprotonation by deuteroxide ion.

A final option (D4, Scheme 3) is compatible with the occurrence of acid catalysis in the case of the N-pyridyl salt only, and also supports Path C as the main mechanism for deuterium exchange at lower pDs for the other triazolium salts \( 6a, 11 \) and \( 12 \) rather than Path B. In this mechanism, observed acid catalysis can be explained by N-protonation on the triazolium ring accompanied by intramolecular deprotonation at C(3) by the pyridyl nitrogen. This intramolecular deprotonation could be direct or may involve one or more solvent molecules. As this option is not available to the other substrates \( 6a, 11 \) and \( 12 \), it could provide an explanation for the singular occurrence of acid catalysis in the case of N-pyridyl substrate 13 only.
The log $k_{ex} - pD$ profile for $N$-pyrimidinyl salt 14 (Figure 2, ◊) is comparable to those for 11 and 12 displaying an increase of rate constants for exchange with $pD$ in the whole region studied and no acid catalysis of deuterium exchange is observed at lower pDs. This suggests that intramolecular catalysis, through C(3) deprotonation by the adjacent pyrimidine ring, is not occurring in this case, which is logical given the much decreased basicity of a simple monocyclic pyrimidine relative to a pyridine nitrogen ($pK_a$s of 5.1 and 1.1 for N-protonated pyridinium and pyrimidinium ions, respectively).\[26\] The data for $N$-pyrimidinyl salt 14 fits well to Eqns. (2) or (3), and the resulting values for $k_{DO}$, $K_{aN}$, and, $k_{D2O}$ or $k_{ DO'}$ are shown in Tables 1 and 2. Significantly, the observed $pK_a^N = 0.36$ for the $N$-pyrimidinyl substrate 14 is very similar to that observed for $N$-pyridyl substrate 13 ($pK_a^N = -0.05$), and provides further evidence that protonation occurs on the triazolium N(1) rather than the pyrimidine ring, which would be expected to yield more different $pK_a$s. This lends further support to reaction via Path C as the dominant mechanism for all salts, except $N$-pyridyl triazolium ion 13, at lower pDs.

**Estimation of Carbon acid $pK_a$ Values**

The carbon acid $pK_a$ values for deprotonation at C(3) for monocationic triazolium salts 11-14 may be determined using Eqn. (5), which is derived for Scheme 4.\[18, 20-22, 27-31\] In this equation, $k_{HO}$ (M$^{-1}$s$^{-1}$) is the second order rate constant for deprotonation at C(3) by hydroxide ion, which may be calculated from the corresponding $k_{DO}$ value using a value of $k_{HO}/k_{DO} = 2.4^{[32]}$ for the secondary solvent isotope effect on the basicity of HO$^-$ in H$_2$O versus DO$^-$ in D$_2$O. As discussed previously,\[18, 20, 21\] the absence of significant general base catalysis of exchange provides evidence that the reverse protonation of the triazol-3-ylidene 7 by water is equal or close to the limiting rate constant for the physical process of dielectric relaxation of solvent ($k_{HOH} \leq k_{reorg} = 10^{11}$ s$^{-1}$\[33, 34\]).

$$pK_a = pK_w + \log \frac{k_{HOH}}{k_{HO}}$$  \hspace{1cm} (5)
Scheme 4 Equilibrium for deprotonation by hydroxide of triazolium ions 6 at C(3).

\[
\begin{align*}
\text{HO}^- & \quad + \quad \text{\begin{tikzpicture}[baseline = -0.5ex]
        \node at (0,0) [shape=circle,draw, thick, fill = white, minimum size = 0.75cm] (c) {
            \begin{array}{c}
            \text{N} \\
            \text{X} \\
            \text{N}^- \text{Ar}
            \end{array}
        \end{tikzpicture}} \\
\rightleftharpoons & \quad k_{\text{HO}} \quad \quad k_{\text{HOH}} \\
\text{H}_2\text{O} & \quad + \quad \text{\begin{tikzpicture}[baseline = -0.5ex]
        \node at (0,0) [shape=circle,draw, thick, fill = white, minimum size = 0.75cm] (c) {
            \begin{array}{c}
            \text{N} \\
            \text{N}^- \text{Ar}
            \end{array}
        \end{tikzpicture}}
\end{align*}
\]

The C(3)-H pKₐ values for triazolium salts 11-14 are similar and range from 16.7-17.3. The values are comparable to those estimated for related thiazolium ions (c.f. 15), however, are substantially lower than our previously published values for the conjugate acids of imidazole-2-ylidenes 2, imidazolin-2-ylidenes 3, and trihydropyrimidin-2-ylidenes. This is due to the presence of the additional electron withdrawing ring nitrogen, which increases the stability of the formally neutral NHC 7 relatively to the cationic conjugate acid 6. This large in-plane electron withdrawing effect of nitrogen is relatively common in heterocyclic systems. As mentioned earlier, the pKₐ of N-protonated pyrimidine is 4 units lower than for the pyridinium ion due to the additional ring nitrogen atom in the former system.

The estimated \(k_{\text{DO}}\)' values for C(3)-deprotonation of N-protonated 6a, 11, 12 and 14 by deuter oxide ion (Table 2) are at the diffusional limit. The new \(k_{\text{DO}}\)' data for 11, 12 and 14, are all safely within error of typical bimolecular values for diffusion of small molecules in solution (\(k_d \sim 5 \times 10^9 \text{ M}^{-1}\text{s}^{-1}\)). This provides confidence in a stepwise rather than concerted mechanism for deuterium exchange at C(3) of the dicationic salt, via a distinct monocationic NHC intermediate, as shown in Scheme 1 (Path C). To our knowledge, a monocationic NHC 9, or a N1-alkylated analogue, has not been directly isolated to date, and these additional results for 11, 12 and 14 provide evidence for the transient formation of these species in aqueous solution under acidic conditions.

The C(3)-carbon acid pKₐ values for N(1)-protonated dicationic triazolium salts (c.f. 8, Scheme 1) would be predicted to be substantially lower than for monocationic triazolium ions 6. It is predicted that the reverse protonation of the monocationic NHCs (c.f. 9) will fall below the upper limiting rate constant for protonation by solvent (\(k_{\text{reorg}} = 10^{11} \text{ s}^{-1}\)). Using an average value of \(k_{\text{DO}} = 5 \times 10^9 \text{ M}^{-1}\text{s}^{-1}\) together with \(k_{\text{HOH}} \leq 10^{11} \text{ s}^{-1}\) in Eqn. (5) yields an upper limit estimate of pKₐ ≤
15.3 for the C(3)-carbon acidity of a dicationic triazolium ions. These pKₐs establish the conjugate acids 8 of monocationic carbenes 9 as the most acidic of all NHC families studied to date in aqueous solution.

CONCLUSIONS
Our studies of the deuterium exchange reactions of ortho-disubstituted triazolium salts 11-12 provides additional evidence for formal 2-heteroatom donor effects on pKₐ values at N(1). In particular, there is a marked change in the dependence of log k_{ex} values on pD under more acidic conditions closely similar to data for 6a and more significant than for 6b-6f where the latter have only hydrogens or methyl groups rather than halogens in the 2-position. Although the pD profiles for all the triazolium ions 6a-f and 11-12 are very similar above pD 1.5 yielding k_{DO} values within ~10-fold of each other, the altered dependence on pD under more acidic conditions is more dominant for 2-halo-substituted ions 6a, 11 and 12 than for 6b-6f. The calculated pKₐ values decrease in the order F > Br > Cl although the difference is very small across the series. By contrast, the corresponding C(3)-carbon acid pKₐs increase across this series as a result of a normal electron-withdrawing inductive effect of these substituents. The donor effect on pKₐ, which favours protonation at N(1), may be to suppress unfavourable electrostatic interactions between N(1) and spacially proximal N-aryl ortho-heteroatoms, or, could be a result of stabilizing through-space N⁺-H…ortho-X interactions in the N-protonated salt. The present study also reveals unique substituent effects for the N-(2-pyridyl)-triazolium system 13, which shows distinct acid catalysis of deuterium exchange at lower pD values. This data is best explained by invoking an intramolecular general base role for the N-(2-pyridyl) substituent in conjunction with N1-protonation on the triazolium ring. Overall, these results highlight the varying roles of ortho-heteroatoms in influencing the chemical behavior of widely-used triazolium salts in organic catalysis.

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REFERENCES


Figure 1. pD-rate profiles for the deuterium exchange reactions of the C(3)-proton of triazolium salts 11 (▲) and 12 (▼) in D$_2$O at 25 °C and $I = 1.0$ (KCl). Also plotted for comparison are log $k_{ex}$ – pD data taken from R. S. Massey et al.$^{[21]}$ for the deuterium exchange reactions of triazolium salts 6a (●) and 6d (■). The solid lines show the fits of the data at ionic strength, $I = 1.0$, to Eqn. (3) except for 6d$^{[21]}$ for which data is fit to an equation allowing for only a first order dependence on DO'. For triazolium salt 11 and 12, extra datapoints (▲ and ▼) were obtained in 2 M DCl (shown as open symbols on the same profiles, as for 6a additional data points$^{[21]}$ in 1.2 and 2 M DCl).
Figure 2. pD-rate profiles for the deuterium exchange reactions of the C(3)-proton of triazolium salts 13 (♦) and 14 (◇) in D₂O at 25 °C and I = 1.0 (KCl). Also plotted for comparison are log $k_{ex}$ – pD data taken from R. S. Massey et al.\textsuperscript{[21]} for the deuterium exchange reactions of triazolium salts 6a (●) and 6d (■). The solid lines show the fits of the data to Eqn. (3) for 6a and 14 and Eqn. (4) for 13. For 6d,\textsuperscript{[21]} the data is fit to an equation allowing for only a first order dependence on DO⁻.
Table 1  Second order rate constants for deuteroxide-catalysed hydrogen-deuterium exchange at C(3) (\(k_{DO}, \text{M}^{-1}\text{s}^{-1}\)), carbon acid \(pK_a^{C3}\) and \(pK_a^N\) values in aqueous solution at 25°C and ionic strength, \(I = 1.0\) (KCl).

<table>
<thead>
<tr>
<th>Salt</th>
<th>(k_{DO} (\text{M}^{-1}\text{s}^{-1}))</th>
<th>(pK_a^{C3})</th>
<th>(K_a^N (\text{M}))</th>
<th>(pK_a^N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>(4.29 (\pm 0.13) \times 10^8)</td>
<td>16.7</td>
<td>1.1 (\pm 0.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>12</td>
<td>(2.71 (\pm 0.12) \times 10^8)</td>
<td>16.9</td>
<td>1.3 (\pm 1.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>13</td>
<td>(1.05 (\pm 0.05) \times 10^8)</td>
<td>17.3</td>
<td>0.9 (\pm 0.4)</td>
<td>-0.05</td>
</tr>
<tr>
<td>14</td>
<td>(1.07 (\pm 0.03) \times 10^8)</td>
<td>17.3</td>
<td>2.3 (\pm 1.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>6a</td>
<td>(6.82 (\pm 0.25) \times 10^8)</td>
<td>16.5</td>
<td>1.5 (\pm 0.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>6d</td>
<td>(6.82 (\pm 0.13) \times 10^7)</td>
<td>17.5</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)Values of \(k_{DO} (\text{M}^{-1}\text{s}^{-1})\) obtained by fitting \(\log k_{ex} - pD\) data to Eqn. (2) or (3). \(^b\)Taken from R. S. Massey et al. \(^c\)\(pK_a^{C3}\) values obtained by application of Eqn. (5). \(^d\)Values of \(K_a^N (\text{M})\) obtained by fitting \(\log k_{ex} - pD\) data to Eqn. (2) or (3).

Table 2  Predicted rate constants for \(k_{D2O}, k_{DO}'\) or \(k'\) based on kinetic fitting.

<table>
<thead>
<tr>
<th>Salt</th>
<th>(k_{D2O} (\text{s}^{-1}))</th>
<th>(k_{DO}' (\text{M}^{-1}\text{s}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>(2.0 \times 10^{-5} (\pm 3.8 \times 10^{-6}))</td>
<td>(1.2 \times 10^{10} (\pm 2.2 \times 10^{9}))</td>
</tr>
<tr>
<td>12</td>
<td>(8.0 \times 10^{-9} (\pm 6.6 \times 10^{-6}))</td>
<td>(5.7 \times 10^{9} (\pm 4.7 \times 10^{9}))</td>
</tr>
<tr>
<td>14</td>
<td>(4.7 \times 10^{-6} (\pm 2.6 \times 10^{-6}))</td>
<td>(5.9 \times 10^{9} (\pm 3.3 \times 10^{9}))</td>
</tr>
<tr>
<td>6a</td>
<td>(6.1 \times 10^{-5} (\pm 3.6 \times 10^{-7}))</td>
<td>(3.3 \times 10^{10} (\pm 2.0 \times 10^{9}))</td>
</tr>
<tr>
<td>13</td>
<td>(1.4 \times 10^{-4} (\pm 4.3 \times 10^{-5}))</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)Values of \(k_{D2O} (\text{s}^{-1})\) obtained by fitting \(\log k_{ex} - pD\) data to Eqn. (2). \(^b\)Taken from R. S. Massey et al. \(^c\)Value of \(k' (\text{s}^{-1})\) obtained by fitting \(\log k_{ex} - pD\) data to Eqn. (4). \(^d\)Values of \(k_{DO}' (\text{M}^{-1}\text{s}^{-1})\) obtained by fitting \(\log k_{ex} - pD\) data to Eqn. (3).